REMARKS

Claims 1-4, 8-11, 15-17, 21-24, 28-29, 31-36, 40-45 and 48-49 were pending in the application. Claims 1, 8, 21, 28, 32, 33, 36, 40, 42-45 and 49 have been amended. New claims 50-51 have been added. Accordingly, upon entry of the amendments presented herein, claims 1-4, 8-11, 15-17, 21-24, 28-29, 31-36, 40-44 and 48-51 will remain pending in the application.

No new matter has been added. Support for the amendments to the claims can be found in the claims and throughout the specification as originally filed. In particular, support for the recitation of "a disorder in which TNFα activity is detrimental, wherein the disorder is selected from the group consisting of an autoimmune disease, infectious disease, transplant rejection, malignancy, pulmonary disorder, intestinal disorder, cardiovascular disorder, metabolic disease, liver disease, kidney disease, inflammatory disease, disorders associated with degenerative bone and joint disease, and disorders associated with reperfusion injury" in new claims 50-51 can be found at least at pages 8-16 of the specification.

Amendments to and cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and were done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Acknowledgement of the Withdrawal of Previous Rejections

Applicants gratefully acknowledge the withdrawal of: (a) the previous rejection under 35 U.S.C. § 112, second paragraph; (b) the previous rejection under 35 U.S.C. § 112, first paragraph for lack of enablement; and (c) the previous rejection under 35 U.S.C. § 112, first paragraph for lack of written description.

Rejection of Claims 1-4, 8-11, 15-17, 21-24, 28-29, 31-36, 40-45 and 48-49

Under 35 U.S.C. 112, First Paragraph, Written Description

The Examiner has rejected claims 1-4, 8-11, 15-17, 21-24, 28-29, 31-36, 40-45 and 48-49 under 35 U.S.C. 112, first paragraph as containing new matter. Specifically, the Examiner is of the opinion that "the specification as originally filed does not provide support for a 'dose

of 0.01 – 0.1 mg/kg' of anti-TNFα antibody to treat 'a disorder in which TNFα activity is detrimental', such as arthritis or rheumatoid arthritis, or the symptoms associated therewith."

Applicants respectfully traverse this rejection. Applicants submit that the specification provides sufficient description so as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, were in possession of the claimed invention.

The fundamental factual inquiry in a written description rejection is whether the claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed. The subject matter of the claim ***need not be described literally*** (*i.e.*, using the same terms or in *haec verba*) in order for the disclosure to satisfy the written description requirement. MPEP § 2163.02.

Applicants submit that, based on the teachings in Applicants' specification and the knowledge in the art at the time of filing, one of ordinary skill in the art would have recognized that Applicants were in possession of the invention as presently claimed. Indeed, the specification provides ample teachings or "blazemarks" of the claimed "low dose of 0.01 – 0.1 mg/kg" of an anti-TNFα antibody, or antigen-binding portion thereof, to treat a disorder in which TNFα activity is detrimental. To begin with, **express support for the specific range** may be found in Table 2 at page 29 of the specification. Moreover, Applicants teach at page 19, first paragraph, of the specification that

> [i]n one embodiment of the invention, the therapeutically effective amount of an anti-TNFα antibody is a low dose. In one embodiment, the low dose of the antibody administered to a subject suffering from a disorder in which TNFα is detrimental, is ***between about 0.01-2.0 mg/kg***, about 0.06 - 1.9 mg/kg, about ***0.11*** - 1.8 mg/kg, about 0.16 - 1.7 mg/kg, about 0.21 - 1.6 mg/kg, about 0.26 - 1.5 mg/kg, about 0.31 - 1.4 mg/kg, about 0.36 - 1.3 mg/kg, about 0.41 - 1.2 mg/kg, about 0.46 - 1.1 mg/kg, about 0.51 - 1.0 mg/kg, about 0.56 - 0.9 mg/kg, about 0.61 - 0.8 mg/kg, and about 0.66 - 0.7 mg/kg. In a preferred embodiment, the antibody is D2E7. ***Ranges intermediate to the above recited dosages***, e.g. about 0.17 - 1.65 mg/kg ***are also intended to be part of this invention. For example, ranges of values using a combination of any of the above recited values as upper and/or lower limits are intended to be included.***

A dose of 0.01 – 0.1 mg/kg is, as taught in the specification, a "range intermediate to" the range 0.01 – 2.0 mg/kg. Moreover, in Example 1 and in the description of the figures, Applicants

expressly disclose the administration of anti-TNFα antibodies (including D2E7 and Remicade) to mice over a range of doses from 0.01 to 10 mg/kg, ***including the specific doses of 0.1 mg/kg and 0.01 mg/kg***. For example, the description of Figures 1 and 2 in the specification discloses the following:

> ***Figure 1 shows arthritic scores of each mouse in the treatment groups receiving different doses of D2E7.*** Arthritic scores were recorded weekly starting at 1 week of age. For each treatment group, mean ± standard error of arthritis scores are indicated in the graph. The ***treatment groups were as follows***: Control group: 11 female, 9 male mice (n=20); 10 mg/kg dose group: 2 female, 2 male mice (n=4); 5 mg/kg dose group: 6 female, 1 male mice (n=7); 1 mg/kg dose group: 5 female, 3 male mice (n=8); 0.5 mg/kg dose group: 3 female, 2 male mice (n=5); ***0.1 mg/kg dose group***: 3 female, 3 male mice (n=6); ***0.01 mg/kg dose group***: 4 female, 2 male mice (n=6).

> ***Figure 2 shows arthritic scores of each mouse in the treatment groups receiving different doses of Remicade® (infliximab).*** Arthritic scores were recorded weekly starting at 1 week of age. For each treatment group, mean ± standard error of arthritis scores are indicated in the graph. The treatment groups were as follows: Control group: 11 female, 9 male mice (n=20); 10 mg/kg dose group: 4 female, 1 male mice (n=5); 5 mg/kg dose group: 3 female, 4 male mice (n=7); 1 mg/kg dose group: 6 female, 2 male mice (n=8); 0.5 mg/kg dose group: 4 female, 2 male mice (n=6); ***0.1 mg/kg dose group***: 1 female, 4 male mice (n=5); ***0.01 mg/kg dose group***: 2 female, 3 male mice (n=5).

Furthermore, Applicants provide data demonstrating the effectiveness of the anti-TNFα inhibitors (including D2E7 and Remicade) at the claimed dose range. For example, Figure 5 depicts the evaluation of the effects of anti-TNFα inhibitors (including D2E7 and Remicade) administered over the aforementioned range of doses, including ***0.01 mg/kg*** and ***0.1 mg/kg***, on relieving symptoms commonly associated with arthritis (*e.g.*, inflammation, vascularity, cartilage erosion and bone erosion) in mice, as evidenced by an analysis of microscopic signs of disease activity in the arthritic joints of the mice. Table 2 at page 29 of the specification discloses the approximate ED_{50} (the amount of anti-TNFα inhibitor required ***to effect 50% of the animals***) determined for the treatment of the arthritic symptoms by the anti-TNFα inhibitors. For example, the approximate ED_{50} for D2E7 is ***0.1 mg/kg*** for the treatment of inflammation and vascularity and ***between 0.01 and 0.1 mg/kg*** for the treatment of cartilage and bone erosion.

In summary, Applicants submit that the ordinary skilled artisan, armed with the ***collective teachings*** of the specification, would have understood that Applicants were in possession of a low dose of 0.01 – 0.1 mg/kg of an anti-TNFα antibody, or antigen-binding portion thereof, at the time of filing of the present application. Accordingly, Applicants respectfully submit that this rejection of claims 1-4, 8-11, 15-17, 21-24, 28-29, 31-36, 40-45 and 48-49 under 35 U.S.C. 112, first paragraph, for lack of written description is improper and request that it be reconsidered and withdrawn.

***Rejection of Claims* 1-4, 8-11, 15-17, 21-24, 28-29, 31-36, 40-45 and 48-49**
Under 35 U.S.C. § 102(b)

The Examiner has maintained the rejection of claims 1-4, 8-11, 15-17, 21-24, 28-29, 31-36, 40-45 and 48-49 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 6,258,562 in the name of Salfeld *et al.* (hereinafter referred to as "the '562 patent"). In particular, the Examiner is of the opinion that "Salfeld teaches [that a] dosage of anti-TNFα antibody, or an antigen binding portion thereof, ***within the range of 0.1-20mg/kg***, is effective for treating rheumatoid arthritis," and that "the ***effective dose range of Salfeld,*** '0.1-20 mg/kg', ***recites the discrete dosage value of '0.1'*** which is also recited in the instant claims." The Examiner highlights M.P.E.P. § 2131.03 (II), which specifies that the standard for disclosing claimed subject matter in the cited reference with "sufficient specificity" is similar to that of "clearly envisaging" a species from a generic teaching. The Examiner continues that "one of skill in the art reading Salfeld would not only 'clearly envisage', but would instantly recognize that '0.1' mg/kg is an effective dose of anti-TNFα antibody, or an antigen binding portion thereof, for treating rheumatoid arthritis." Based on the foregoing, the Examiner concludes that "Salfeld anticipates the instant claims."

Applicants traverse this rejection and maintain that the '562 patent fails to teach or suggest each and every element of the claimed invention in accordance with 35 U.S.C. §102(b). Applicants respectfully submit that the Examiner is incorrectly interpreting MPEP § 2131.03 cited by Applicants. MPEP § 2131.03 specifically provides guidelines for determining whether a particular ***range*** taught in the prior art anticipates a claimed ***range***, where the prior art range either ***touches, overlaps*** or ***falls within*** the claimed range:

> When the prior art discloses a ***range*** which ***touches, overlaps*** or is ***within*** the claimed range, but ***no specific examples falling within the claimed range are disclosed***, a case by case determination must be made as to anticipation. In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with "sufficient specificity to constitute an anticipation under the statute." What constitutes a "sufficient specificity" is fact dependent. If the claims are directed to a narrow range, the reference teaches a broad range, and there is evidence of unexpected results within the claimed narrow range, depending on the other facts of the case, it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims. The unexpected results may also render the claims unobvious. (See M.P.E.P. § 2131.03; *emphasis added*).

The Examiner alleges that the '562 patent discloses a "discrete dose of 0.1 mg/kg" that falls within the claimed range, and concludes that the '562 patent anticipates the claimed range. The Examiner appears to be incorrectly suggesting that every possible value within a ***range*** taught in the prior art (for example, the values 5, 6 and 7 within the range 4-8) constitutes a "specific example," i.e., "***discrete value,***" taught by the prior art which, if falling within the claimed range, would anticipate the claims. Contrary to the Examiner's assertion, a disclosed range does not comprise disclosed discrete values. If one were to apply the Examiner's reasoning to a hypothetical example in which the claimed range is 1-10,000 and the prior art teaches an ***overlapping range*** of 0.1-4, then any number of "discrete values" between 1 and 4 (*e.g.*, 2, 3, 4) would fall within and, thereby, anticipate the claimed range. Similarly, if one applies the Examiner's reasoning to a hypothetical example in which the claimed range is 1-10,000 and the prior art teaches a range of 2-3 that ***falls within*** the claimed range, then any number of "discrete values" between 2 and 3 (*e.g.*, 2, 2.1, 2.2, 2.3) would fall within and, thereby, anticipate the claimed range. ***Such reasoning, if correct, would clearly obviate the need for the M.P.E.P. § 2131.03, which deals specifically with prior art which discloses ranges that touch, overlap or are within the claimed range, but which does not disclose specific examples (i.e., discrete numeric values) falling within the claimed range.***

In the present case, contrary to the Examiner's assertion, the '562 patent teaches only a ***range*** of doses, *i.e.*, ***0.1-20 mg/kg.*** The'562 patent does not teach a specific example, *i.e.*, a ***discrete value***, of 0.1 mg/kg, for the dose. Therefore, the '562 patent discloses a dose range (0.1-20 mg/kg) which ***touches*** the claimed range (0.01-0.1 mg/kg), since the '562 patent and the claimed range share "0.1 mg/kg" as the minimum and maximum dose, respectively, of the

respective dose ranges. M.P.E.P. § 2131.03 is directed specifically to this unique situation, *i.e.*, a situation in which the prior art and the claims are directed to a particular ***range of values***, rather than discrete values.

M.P.E.P. § 2131.03 specifies that in order to anticipate the claims, the claimed subject matter must be disclosed in the reference with "sufficient specificity to constitute an anticipation under the statute." M.P.E.P. § 2131.03 further specifies that "***if the claims are directed to a narrow range, the [prior art] reference teaches a broad range, and there is evidence of unexpected results within the claimed narrow range,*** depending on the other facts of the case, ***it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims.***" As indicated previously, the pending claims are directed to a narrow range of 0.01-0.1 mg/kg, while the '562 patent discloses a much broader range of 0.1-20 mg/kg. Moreover, the specification discloses the unexpected discovery that the claimed low dose range of 0.01-0.1 mg/kg of a TNFα inhibitor, *e.g.*, an anti-TNFα antibody or antigen-binding portion thereof, can be effective in treating disorders in which TNFα activity is detrimental and alleviating symptoms associated with these disorders. Applicants teach in the specification various benefits associated with administering the claimed low doses of a TNFα inhibitor, *e.g.*, an anti-TNFα antibody or antigen-binding portion thereof, including improvement in cartilage erosion (see, for example, Table 2 at page 29 of the specification.) Applicants also teach in the specification that low doses of a TNFα inhibitor, *e.g.*, an anti-TNFα antibody or antigen-binding portion thereof, may be advantageous as they may decrease side effects and may decrease the frequency of administration associated with the normally prescribed dose (see, for example, page 7, lines 20-22 of the specification).

In view of the foregoing, it is evident that the '562 patent fails to teach or suggest the claimed narrow range of 0.01-0.1 mg/kg with ***sufficient specificity*** to constitute an anticipation of the pending claims. Accordingly, Applicants respectfully request that the rejection of claims 1-49 under 35 U.S.C. 102(b) as lacking novelty over the '562 patent be reconsidered and withdrawn.

***Rejection of Claims* 1-4, 8-11, 15-17, 21-24, 28-29, 31-36, 40-45 and 48-49**
Under 35 U.S.C. § 102(e)

The Examiner has maintained the rejection of claims 1-4, 8-11, 15-17, 21-24, 28-29, 31-36, 40-45 and 48-49 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,509,015 in the name of Salfeld *et al.* (hereinafter referred to as "the '015 patent") for the same reasons as discussed above with respect to the '562 patent.

Applicants respectfully traverse this rejection and maintain that the '015 patent fails to teach or suggest each and every element of the claimed invention in accordance with 35 U.S.C. §102(e). Similar to the '562 patent, the '015 patent fails to anticipate the claimed invention in that there is no teaching or suggestion in the '015 patent to use a low dose range ***of 0.01-0.1 mg/kg*** of a TNFα inhibitor. Indeed, there is no teaching or suggestion in the '015 patent to consider any doses which appear less efficacious in standard assays than saturating doses. As discussed above, when "the prior art discloses a range which ***touches***... the claimed range, but ***no specific examples*** falling within the claimed range are disclosed, a case by case determination must be made as to anticipation." "If the claims are directed to a ***narrow range,*** the [prior art] reference teaches a ***broad range,*** and there is ***evidence of unexpected results within the claimed narrow range,*** depending on the other facts of the case, ***it may be reasonable to conclude that the narrow range is not disclosed with 'sufficient specificity' to constitute an anticipation of the claims.***" (See M.P.E.P. § 2131.03; *emphasis added*).

Similar to the '562 patent, the '015 patent discloses a dose range (0.1-20 mg/kg) which ***touches*** the claimed range (0.01-0.1 mg/kg), but fails to disclose a ***specific example*** falling within the claimed range. Further, the pending claims are directed to a ***narrow*** range of 0.01-0.1 mg/kg, while the '015 patent discloses a much ***broader*** range of 0.1-20 mg/kg. Finally, the instant specification discloses the ***unexpected discovery*** that the claimed low dose of 0.01-0.1 mg/kg of a TNFα inhibitor, *e.g.*, an anti-TNFα antibody or antigen-binding portion thereof, can be effective in treating the disorders in which TNFα activity is detrimental and alleviating symptoms associated with these disorders. Thus, the '015 patent fails to teach or suggest the claimed narrow range of 0.01-0.1mg/kg with sufficient specificity to constitute an anticipation of the claims.

In view of the foregoing, Applicants submit that this rejection of claims 1-4, 8-11, 15-17, 21-24, 28-29, 31-36, 40-45 and 48-49 under §102(e) over the '015 patent is improper and respectfully request that it be reconsidered and withdrawn.

***Rejection of Claims* 1-4, 8-11, 15-17, 21-24, 28-29, 31 and 43**
Under 35 U.S.C. § 102(b)

The Examiner has rejected of claims 1-4, 8-11, 15-17, 21-24, 28-29, 31 and 43 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,994,510 in the name of Adair *et al.* (hereinafter referred to as "the '510 patent"). The Examiner relies on the '510 patent for teaching "a method of treating a disorder in which TNFα activity is detrimental, for example, rheumatoid arthritis, and the symptoms associated therewith, comprising administering an anti-TNFα antibody, for example CDP571, or an antigen binding portion thereof, as a stand alone agent or with an additional therapeutic agent." The Examiner further relies on the '510 patent for teaching that "where the product is for treatment or prophylaxis of septic shock suitable doses of antibody to TNF lie in the range **0.001**-30 mg/kg/day, preferably **0.01**-10 mg/kg/day and particularly preferably **0.1**-2 mg/kg/day."

Applicants respectfully traverse this rejection on the grounds that the '510 patent fails to teach or suggest each and every element of the claimed invention in accordance with 35 U.S.C. §102(b). For a prior art reference to anticipate a claimed invention under 35 U.S.C. 102, the prior art must teach *each and every element* of the claimed invention. *Lewmar Marine v. Barient*, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Claims 1-4, 8-11, 28-29 and 31

Claim 1, and claims 2-4, and 31 in part, which depend therefrom, as currently amended, are directed to a method for treating a disorder in which TNFα activity is detrimental comprising administering to a subject an effective amount of a ***human*** anti-TNFα antibody, or an antigen-binding portion thereof, in a low dose of 0.01-0.1 mg/kg, such that the disorder is treated. Claim 8, and claims 9-11, and 31 in part, which depend therefrom, as currently amended, are directed to a low dose method for alleviating symptoms associated with a disorder in which TNF activity is detrimental, comprising administering a low dose of 0.01-0.1 mg/kg of a ***human*** anti-TNFα antibody, or an antigen-bdining portion thereof, to a subject suffering from said disorder, such

that the symptoms are alleviated. Claim 28, and claim 29, which depends therefrom, as currently amended, are directed to a method of sequestering TNFα into complexes in a subject suffering from a disorder in which TNFα activity is detrimental, by administering a low dose of 0.01 – 0.1 mg/kg of a ***human*** anti-TNFα antibody, or an antigen-binding portion thereof, to the subject, such that TNFα is sequestered into complexes.

The '510 patent is directed to ***humanized*** anti-TNFα antibodies and their use in the treatment of disorders associated with undesirably high levels of TNFα. The '510 patent fails to teach or suggest ***human*** anti-TNFα antibodies, as required by claims 1, 8 and 28 (and the claims which depend therefrom) as currently amended. Accordingly, the '510 patent fails to anticipate claims 1-4, 8-11, 28-29 and 31.

Claims 15-17, 21-24, 31 and 43

Claim 15, and claims 26-27 and 31, which depend therefrom, are directed to a method for treating ***arthritis*** comprising administering to a subject an effective amount of an anti-TNFα antibody, or antigen-binding portion thereof, in a **low dose of 0.01 – 0.1 mg/kg**, such that the arthritis is treated. Claim 21, and claims 22-24 and 31, which depend therefrom, are directed to a method for alleviating ***symptoms associated with arthritis*** comprising administering to a subject an effective amount of an anti-TNFα antibody, or antigen-binding portion thereof, in a ***low dose of 0.01 – 0.1 mg/kg,*** such that the symptoms are alleviated.

The '510 patent teaches that "[t]he dose at which the antibody is administered ***depends on the nature of the condition to be treated***, the ***degree to which the TNF to be neutralized is, or is expected to be, raised above a desirable level***, and on ***whether the antibody is being used prophylactically or to treat an existing condition***." The '510 patent teaches that the humanized anti-TNFα antibodies are preferably used in the treatment of ***sepsis or septic-endotoxic shock*** (see column 11, last paragraph) and teaches a ***specific dose*** of humanized anti-TNFα antibodies appropriate only for the treatment of ***septic shock***. In particular, the '510 patent discloses that "where the product is for treatment or prophylaxis of ***septic shock*** suitable doses of antibody to TNF lie in the range 0.001-30 mg/kg/day, preferably 0.01-10 mg/kg/day and particularly preferably 0.1-2 mg/kg/day" (see column 12, lines 51-55). Septic shock and arthritis are ***completely different disorders***. The '510 patent fails to teach or suggest any specific dose for any disorder other than septic shock, let alone a low dose of ***0.01-0.1 mg/kg*** for the ***treatment of arthritis*** or ***symptoms associated with arthritis***, as required by claims 15 and 21, and the claims

which depend therefrom. Accordingly, the '510 patent fails to anticipate claims 15-17, 21-24, 31 and 43.

In view of the foregoing, Applicants respectfully request that the rejection of claims 1-4, 8-11, 15-17, 21-24, 28-29, 31 and 43 under 35 U.S.C. § 102(b) over the '510 patent be reconsidered and withdrawn..

Rejection of Claims 1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45 and 48-49 Under the Doctrine of Obviousness-Type Double Patenting

The Examiner has rejected claims 1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45 and 48-49 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-100 of the '015 patent in view of the '562 patent and the '510 patent. The Examiner relies on the claims of the '015 patent as being "directed to a method of treating rheumatoid arthritis by administering an anti-TNFα antibody, alone or in combination with additional therapeutic agents." The Examiner acknowledges that the presently pending claims differ from the "reference teachings" in the recitation of a "dose of 0.01-0.1 mg/kg." The Examiner further relies on the '562 patent as teaching that "an effective dose of anti-TNFα antibody is for example, 0.1 mg/kg" and the '510 patent as teaching that "an effective dose of anti-TNFα antibody is for example, 0.001, 0.01 or 0.1 mg/kg." The Examiner concludes that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other."

Applicants respectfully traverse the aforementioned obviousness-type double patenting rejection on the grounds that the claimed low dose methods would not have been obvious to one of ordinary skill in the art over the claims of the '015 patent in view of the '562 patent and the '510 patent.

A nonstatutory basis exists for a double patenting rejection when the claimed invention is an obvious variation of an invention in an issued patent (M.P.E.P. § 804(B)(1)). Accordingly, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). To establish a *prima facie* case of obviousness, it is necessary for the

Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been ***motivated*** to make the claimed invention and would have had a reasonable ***expectation of success*** in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when considering prior art disclosing a range which "touches" the claimed range, "unexpected results [within the claimed narrow range] may... render the claims unobvious" (see M.P.E.P. § 2131.03).

The claimed methods are unique in that they embody Applicants' unexpected discovery that low doses, *e.g.*, 0.01-0.1 mg/kg, of TNFα inhibitors can be effective in treating the disorders in which TNFα activity is detrimental and alleviating symptoms associated with these disorders. Applicants teach in the specification various benefits associated with administering low doses of the TNFα inhibitors, including improvement in cartilage erosion (see, for example, Table 2 at page 29 of the specification). Applicants also teach in the specification that low doses of a TNFα inhibitor may be advantageous as they may decrease side effects and may decrease the frequency of administration associated with the normally prescribed dose (see, for example, page 7, lines 20-22 of the specification). In contrast, the claims of the '015 patent are directed to methods for treating rheumatoid arthritis by administering a human anti-TNFα antibody. As acknowledged by the Examiner, the claims of the '015 patent fail to teach or suggest a low dose of 0.01 – 0.1 mg/kg of a human anti-TNFα antibody.

The '562 patent fails to make up for this deficiency. The '562 patent provides general guidance with regard to normally prescribed dosing. The '562 patent fails to teach or suggest methods which use a low dose of 0.01-0.1 mg/kg of a TNFα inhibitor. In particular, as acknowledged by the Examiner, the '562 patent teaches that a therapeutically effective dose range for human anti-TNFα antibodies is 0.1-20 mg/kg. Thus, the '562 patent,similar to the claims of the '015 patent, fails to teach or suggest methods which use a ***low dose of 0.01-0.1 mg/kg of an anti-TNFα antibody or antigen-binding portion thereof.*** Moreover, one of ordinary skill in the art would not have been motivated to arrive at the claimed invention, *i.e.*, to select the claimed dosage range of 0.01 to 0.1 mg/kg, based on the disclosure of the '562 patent,

because the '562 patent already teaches the successful inhibition of human TNFα activity using a dosage range of 0.1-20 mg/kg. Further, as indicated above, ***when considering prior art disclosing a range which "touches" the claimed range, "unexpected results [within the claimed narrow range] may... render the claims unobvious***" (see M.P.E.P. §2131.03). In the present case, while the '562 patent discloses a dose range which "touches" the claimed dose range of 0.01-0.1 mg/kg, the unexpected results provided by Applicants further prove that the pending claims are unobvious over the teachings of the '562 patent.

The '510 patent, like the '562 patent, fails to make up for the deficiencies of the '015 patent. The '510 patent is directed to ***humanized*** anti-TNFα antibodies and their use in the treatment of disorders associated with undesirably high levels of TNFα. In particular, the '510 patent discloses that "where the product is for treatment or prophylaxis of ***septic shock*** suitable doses of [humanized] antibody to TNF lie in the range 0.001-30 mg/kg/day, preferably 0.01-10 mg/kg/day and ***particularly preferably 0.1-2 mg/kg/day***" (see column 12, lines 51-55). The '510 patent fails to teach or suggest the claimed low dose of 0.01 – 0.1 mg/kg. The '510 patent teaches that the suitable dose of humanized antibody to TNF is ***particularly preferably 0.1-2 mg/kg/day***. Further, the '510 patent provides data indicating that a dose of 1.0 mg/kg is more effective than a 0.1 mg/kg dose in a baboon model for septic shock (see Example 4, column 20, lines 3-10 and Table 1). Thus, the '510 patent ***teaches away*** from the claimed low dose of 0.01-0.1 mg/kg. Moreover, the '510 patent fails to teach or suggest suitable doses for a ***human*** anti-TNFα antibody, as required by pending claims 1, 8 and 28 (and the claims which depend therefrom). Humanized antibodies are ***completely different*** from fully human antibodies. Therefore, one of skill in the art would not have expected that doses suitable for a humanized antibody would be similarly suitable for a fully human antibody. Further, the '510 patent fails to teach or suggest any specific dose for any disorder other than septic shock, let alone a low dose of ***0.01-0.1 mg/kg*** for the ***treatment of arthritis*** or ***symptoms associated with arthritis***, as required by pending claims 15 and 21 (and the claims which depend therefrom). Septic shock and arthritis are ***completely different disorders***. One of skill in the art would have had no expectation that a dose suitable for the treatment of septic shock would similarly be suitable for the treatment of arthiritis. Accordingly, one of skill in the art would not have had the motivation nor a reasonable expectation of success in arriving at the claimed invention based on the teachings of the '510 patent.

In view of the foregoing, it is evident that the claims of the '015 patent in view of the teachings of the '562 patent and the '510 patent fail to render the claimed invention obvious. Accordingly, Applicants respectfully request that the rejection of claims 1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45 and 48-49 under the judicially created doctrine of obviousness-type double patenting be reconsidered and withdrawn.

Provisional Rejection of Claims 1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45 and 48-49 Under the Doctrine of Obviousness-Type Double Patenting

The Examiner has provisionally rejected claims 1-4, 8-11, 15-17, 21-24, 28, 29, 31-36, 40-45 and 48-49 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 15-19 of co-pending U.S. Application No. 11/233,252 (hereinafter referred to as "the '252 application") and over claims 114-121 and 141-166 of co-pending U.S. Application No. 09/801,185 (hereinafter referred to as "the '185 application"), both in view of the '562 patent and the '510 patent. The Examiner is of the opinion that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other."

Applicants respectfully acknowledge the provisional rejection of these claims. However, since neither claims 15-19 of the '252 application nor claims 114-121 and 141-166 of the '185 application are presently patented or indicated as allowed, Applicants will address this rejection in the co-pending applications.

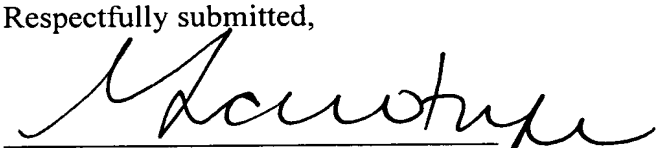
CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

In addition, Applicants include herewith authorization to charge fees associated with new claims and the extension of time with which to respond, to Deposit Account No. 12-0080, under Order No. BBI-190RCE. The Director is also hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to Deposit Account No. 12-0080, under Order No. BBI-190RCE.

Dated: **November 17, 2006**

Respectfully submitted,



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